EXHIBIT 48

51 FR 33992-01
51 FR 33992-01, 1986 WL 108339 (F.R.)
(Cite as: 51 FR 33992)

NOTICES

ENVIRONMENTAL PROTECTION AGENCY

[FRL-2984-1]

Guidelines for Carcinogen Risk Assessment

Wednesday, September 24, 1986

*33992 AGENCY: U.S. Environmental Protection Agency (EPA).

ACTION: Final guidelines for carcinogen risk assessment.

SUMMARY: The U.S. Environmental Protection Agency is today issuing five guidelines for assessing the health risks of environmental pollutants. These are:

Guidelines for Carcinogen Risk Assessment

Guidelines for Estimating Exposures

Guidelines for Mutagenicity Risk Assessment

Guidelines for the Health Assessment of Suspect Developmental Toxicants

Guidelines for the Health Risk Assessment of Chemical Mixtures

This notice contains the Guidelines for Carcinogen Risk Assessment; the other guidelines appear elsewhere in today's Federal Register.

The Guidelines for Carcinogen Risk Assessment (hereafter "Guidelines") are intended to guide Agency evaluation of suspect carcinogens in line with the policies and procedures established in the statutes administered by the EPA. These Guidelines were developed as part of an interoffice guidelines development program under the auspices of the Office of Health and Environmental Assessment (OHEA) in the Agency's Office of Research and Development. They reflect Agency consideration of public and Science Advisory Board (SAB) comments on the Proposed Guidelines for Carcinogen Risk Assessment published November 23, 1984 (49 FR 46294).

This publication completes the first round of risk assessment guidelines development. These Guidelines will be revised, and new guidelines will be developed, as appropriate.

EFFECTIVE DATE: The Guidelines will be effective September 24, 1986.

FOR FURTHER INFORMATION CONTACT: Dr. Robert E. McGaughy, Carcinogen Assessment

Part A: Guidelines for Carcinogen Risk Assessment

I. Introduction

This is the first revision of the 1976 Interim Procedures and Guidelines for Health Risk Assessments of Suspected Carcinogens (U.S. EPA, 1976; Albert et al., 1977). The impetus for this revision is the need to incorporate into these Guidelines the concepts and approaches to carcinogen risk assessment that have been developed during the last ten years. The purpose of these Guidelines is to promote quality and consistency of carcinogen risk assessments within the EPA and to inform those outside the EPA about its approach to carcinogen risk assessment. These Guidelines emphasize the broad but essential aspects of risk assessment that are needed by experts in the various disciplines required (e.g., toxicology, pathology, pharmacology, and statistics) for carcinogen risk assessment. Guidance is given in general terms since the science of carcinogenesis is in a state of rapid advancement, and overly specific approaches may rapidly become obsolete.

These Guidelines describe the general framework to be followed in developing an analysis of carcinogenic risk and some salient principles to be used in evaluating the quality of data and in formulating judgments concerning the nature and magnitude of the cancer hazard from suspect carcinogens. It is the intent of these Guidelines to permit sufficient flexibility to accommodate new knowledge and new assessment methods as they emerge. It is also recognized that there is a need

for new methodology that has not been addressed in this document in a number of areas, e.g., the characterization of uncertainty. As this knowledge and assessment methodology are developed, these Guidelines will be revised whenever appropriate.

A summary of the current state of knowledge in the field of carcinogenesis and a statement of broad scientific principles of carcinogen risk assessment, which was developed by the Office of Science and Technology Policy (OSTP, 1985), forms an important basis for these Guidelines; the format of these Guidelines is similar to that proposed by the National Research Council (NRC) of the National Academy of Sciences in a book entitled Risk Assessment in the Federal Government: Managing the Process (NRC, 1983).

These Guidelines are to be used within the policy framework already provided by applicable EPA statutes and do not alter such policies. These Guidelines provide general directions for analyzing and organizing available data. They do not imply that one kind of data or another is prerequisite for regulatory action to control, prohibit, or allow the use of a carcinogen.

Regulatory decision making involves two components: risk assessment and risk management. Risk assessment defines the adverse health consequences of exposure to toxic agents. The risk assessments will be carried out independently from considerations of the consequences of regulatory action. Risk management combines the risk assessment with the directives of regulatory legislation, together with socioeconomic, technical, political, and other considerations, to reach a decision as to whether or how much to control future exposure to the suspected toxic agents.

Risk assessment includes one or more of the following components: hazard identification, dose-response assessment, exposure assessment, and risk characterization (NRC, 1983).

Hazard identification is a qualitative risk assessment, dealing with the process of determining whether exposure to an agent has the potential to increase the incidence of cancer. For purposes of these Guidelines, both malignant and benign tumors are used in the evaluation of the carcinogenic hazard. The hazard identification component qualitatively answers the question of how likely an agent is to be a human carcinogen.

Traditionally, quantitative risk assessment has been used as an inclusive term to describe all or parts of dose-response assessment, exposure assessment, and risk characterization. Quantitative risk assessment can be a useful general term in some circumstances, but the more explicit terminology developed by the NRC (1983) is usually preferred. The dose-response assessment defines the relationship between the dose of an agent and the probability of induction of a carcinogenic effect. This component usually entails an extrapolation from the generally high doses administered to experimental animals or exposures noted in epidemiologic studies to the exposure levels expected from human contact with the agent in the

environment; it also includes considerations of the validity of these extrapolations.

The exposure assessment identifies populations exposed to the agent, describes their composition and size, and presents the types, magnitudes, frequencies, and durations of exposure to the agent.

***33994** In risk characterization, the results of the exposure assessment and the dose-response assessment are combined to estimate quantitatively the carcinogenic risk. As part of risk characterization, a summary of the strengths and weaknesses in the hazard identification, dose-response assessment, exposure assessment, and the public health risk estimates are presented. Major assumptions, scientific judgments, and, to the extent possible, estimates of the uncertainties embodied in the assessment are also presented, distinguishing clearly between fact, assumption, and science policy.

The National Research Council (NRC, 1983) pointed out that there are many questions encountered in the risk assessment process that are unanswerable given current scientific knowledge. To bridge the uncertainty that exists in these areas where there is no scientific consensus, inferences must be made to ensure that progress continues in the assessment process. The OSTP (1985) reaffirmed this position, and generally left to the regulatory agencies the job of articulating these inferences. Accordingly, the Guidelines incorporate judgmental positions (science policies) based on evaluation of the presently available information and on the regulatory mission of the Agency. The Guidelines are consistent with the principles developed by the OSTP (1985), although in many instances are necessarily more specific.

II. Hazard Identification

A. Overview

The qualitative assessment or hazard identification part of risk assessment contains a review of the relevant biological and chemical information bearing on whether or not an agent may pose a carcinogenic hazard. Since chemical agents seldom occur in a pure state and are often transformed in the body, the review should include available information on contaminants, degradation products, and metabolites.

Studies are evaluated according to sound biological and statistical considerations and procedures. These have been described in several publications (Interagency Regulatory Liaison Group, 1979; OSTP, 1985; Peto et al., 1980; Mantel, 1980; Mantel and Haenszel, 1959; Interdisciplinary Panel on Carcinogenicity, 1984; National Center for Toxicological Research, 1981; National Toxicology Program, 1984; U.S. EPA, 1983a, 1983b, 1983c; Haseman, 1984). Results and conclusions concerning the agent, derived from different types of information, whether indicating positive or negative responses, are melded together into a weight-of-evidence determination. The strength of the evidence supporting a

The summary should present all of the key findings in all of the sections of the qualitative assessment and the interpretive rationale that forms the basis for the conclusion. Assumptions, uncertainties in the evidence, and other factors that may affect the relevance of the evidence to humans should be discussed. The conclusion should present both the weight-of-evidence ranking and a description that brings out the more subtle aspects of the evidence that may not be evident from the ranking alone.

III. Dose-Response Assessment, Exposure Assessment, and Risk Characterization

After data concerning the carcinogenic properties of a substance have been collected, evaluated, and categorized, it is frequently desirable to estimate the likely range of excess cancer risk associated with given levels and conditions of human exposure. The first step of the analysis needed to make such estimations is the development of the likely relationship between dose and response (cancer incidence) in the region of human exposure. This information on dose-response relationships is coupled with information on the nature and magnitude of human exposure to yield an estimate of human risk. The risk-characterization step also includes an interpretation of these estimates in light of the biological, statistical, and exposure assumptions and uncertainties that have arisen throughout the process of assessing risk.

The elements of dose-response assessment are described in section III.A. Guidance on human exposure assessment is provided in another EPA ***33997** document (U.S. EPA, 1986); however, section III.B. of these Guidelines includes a brief description of the specific type of exposure information that is useful for carcinogen risk assessment. Finally, in section III.C. on risk characterization, there is a description of the manner in which risk estimates should be presented so as to be most informative.

It should be emphasized that calculation of quantitative estimates of cancer risk does not require that an agent be carcinogenic in humans. The likelihood that an agent is a human carcinogen is a function of the weight of evidence, as this has been described in the hazard identification section of these Guidelines. It is nevertheless important to present quantitative estimates, appropriately qualified and interpreted, in those circumstances in which there is a reasonable possibility, based on human and animal data, that the agent is carcinogenic in humans.

It should be emphasized in every quantitative risk estimation that the results are uncertain. Uncertainties due to experimental and epidemiologic variability as well as uncertainty in the exposure assessment can be important. There are major uncertainties in extrapolating both from animals to humans and from high to low doses. There are important species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species and strain differences in target-site susceptibility. Human populations are variable with respect to genetic constitution, diet, occupational and home environment, activity patterns, and other cultural factors. Risk estimates should be presented together with the associated hazard assessment (section III.C.3.) to ensure that there is an appre-

ciation of the weight of evidence for carcinogenicity that underlies the quantitative risk estimates.

A. Dose-Response Assessment

1. Selection of Data. As indicated in section II.D., guidance needs to be given by the individuals doing the qualitative assessment (toxicologists, pathologists, pharmacologists, etc.) to those doing the quantitative assessment as to the appropriate data to be used in the dose-response assessment. This is determined by the quality of the data, its relevance to human modes of exposure, and other technical details.

If available, estimates based on adequate human epidemiologic data are preferred over estimates based on animal data. If adequate exposure data exist in a well-designed and well-conducted negative epidemiologic study, it may be possible to obtain an upper-bound estimate of risk from that study. Animal-based estimates, if available, also should be presented.

In the absence of appropriate human studies, data from a species that responds most like humans should be used, if information to this effect exists. Where, for a given agent, several studies are available, which may involve different animal species, strains, and sexes at several doses and by different routes of exposure, the following approach to selecting the data sets is used: (1) The tumor incidence data are separated according to organ site and tumor type. (2) All biologically and statistically acceptable data sets are presented. (3) The range of the risk estimates is presented with due regard to biological relevance (particularly in the case of animal studies) and appropriateness of route of exposure. (4) Because it is possible that human sensitivity is as high as the most sensitive responding animal species, in the absence of evidence to the contrary, the biologically acceptable data set from long-term animal studies showing the greatest sensitivity should generally be given the greatest emphasis, again with due regard to biological and statistical considerations.

When the exposure route in the species from which the dose-response information is obtained differs from the route occurring in environmental exposures, the considerations used in making the route-to-route extrapolation must be carefully described. All assumptions should be presented along with a discussion of the uncertainties in the extrapolation. Whatever procedure is adopted in a given case, it must be consistent with the existing metabolic and pharmacokinetic information on the chemical (e.g., absorption efficiency via the gut and lung, target organ doses, and changes in placental transport throughout gestation for transplacental carcinogens).

Where two or more significantly elevated tumor sites or types are observed in the same study, extrapolations may be conducted on selected sites or types. These selections will be made on biological grounds. To obtain a total estimate of carcinogenic risk, animals with one or more tumor sites or types showing significantly elevated tumor incidence should be pooled and used for extrapolation. The

pooled estimates will generally be used in preference to risk estimates based on single sites or types. Quantitative risk extrapolations will generally not be done on the basis of totals that include tumor sites without statistically significant elevations.

Benign tumors should generally be combined with malignant tumors for risk estimates unless the benign tumors are not considered to have the potential to progress to the associated malignancies of the same histogenic origin. The contribution of the benign tumors, however, to the total risk should be indicated.

2. Choice of Mathematical Extrapolation Model. Since risks at low exposure levels cannot be measured directly either by animal experiments or by epidemiologic studies, a number of mathematical models have been developed to extrapolate from high to low dose. Different extrapolation models, however, may fit the observed data reasonably well but may lead to large differences in the projected risk at low doses.

As was pointed out by OSTP (1985; Principle 26),

No single mathematical procedure is recognized as the most appropriate for low-dose extrapolation in carcinogenesis. When relevant biological evidence on mechanism of action exists (e.g., pharmacokinetics, target organ dose), the models or procedures employed should be consistent with the evidence. When data and information are limited, however, and when much uncertainty exists regarding the mechanism of carcinogenic action, models or procedures which incorporate low-dose linearity are preferred when compatible with the limited information.

At present, mechanisms of the carcinogenesis process are largely unknown and data are generally limited. If a carcinogenic agent acts by accelerating the same carcinogenic process that leads to the background occurrence of cancer, the added effect of the carcinogen at low doses is expected to be virtually linear (Crump et al., 1976).

The Agency will review each assessment as to the evidence on carcinogenesis mechanisms and other biological or statistical evidence that indicates the suitability of a particular extrapolation model. Goodness-of-fit to the experimental observations is not an effective means of discriminating among models (OSTP, 1985). A rationale will be included to justify the use of the chosen model. In the absence of adequate information to the contrary, the linearized multistage procedure will be employed. Where appropriate, the results of using various extrapolation models may be useful for comparison with the linearized multistage procedure. When longitudinal data on tumor development are available, time-to-tumor models may be used.

It should be emphasized that the linearized multistage procedure leads to ***33998** a plausible upper limit to the risk that is consistent with some proposed mechanisms of carcinogenesis. Such an estimate, however, does not necessarily give a realistic prediction of the risk. The true value of the risk is unknown, and may

be as low as zero. The range of risks, defined by the upper limit given by the chosen model and the lower limit which may be as low as zero, should be explicitly stated. An established procedure does not yet exist for making "most likely" or "best" estimates of risk within the range of uncertainty defined by the upper and lower limit estimates. If data and procedures become available, the Agency will also provide "most likely" or "best" estimates of risk. This will be most feasible when human data are available and when exposures are in the dose range of the data.

In certain cases, the linearized multistage procedure cannot be used with the observed data as, for example, when the data are nonmonotonic or flatten out at high doses. In these cases, it may be necessary to make adjustments to achieve low-dose linearity.

When pharmacokinetic or metabolism data are available, or when other substantial evidence on the mechanistic aspects of the carcinogenesis process exists, a low-dose extrapolation model other than the linearized multistage procedure might be considered more appropriate on biological grounds. When a different model is chosen, the risk assessment should clearly discuss the nature and weight of evidence that led to the choice. Considerable uncertainty will remain concerning response at low doses; therefore, in most cases an upper-limit risk estimate using the linearized multistage procedure should also be presented.

3. Equivalent Exposure Units Among Species. Low-dose risk estimates derived from laboratory animal data extrapolated to humans are complicated by a variety of factors that differ among species and potentially affect the response to carcinogens. Included among these factors are differences between humans and experimental test animals with respect to life span, body size, genetic variability, population homogeneity, existence of concurrent disease, pharmacokinetic effects such as metabolism and excretion patterns, and the exposure regimen.

The usual approach for making interspecies comparisons has been to use standardized scaling factors. Commonly employed standardized dosage scales include mg per kg body weight per day, ppm in the diet or water, mg per m 2 body surface area per day, and mg per kg body weight per lifetime. In the absence of comparative toxicological, physiological, metabolic, and pharmacokinetic data for a given suspect carcinogen, the Agency takes the position that the extrapolation on the basis of surface area is considered to be appropriate because certain pharmacological effects commonly scale according to surface area (Dedrick, 1973; Freireich et al., 1966; Pinkel, 1958).

B. Exposure Assessment

In order to obtain a quantitative estimate of the risk, the results of the dose-response assessment must be combined with an estimate of the exposures to which the populations of interest are likely to be subject. While the reader is referred to the Guidelines for Estimating Exposures (U.S. EPA, 1986) for specific details, it is important to convey an appreciation of the impact of the strengths

The summary should present all of the key findings in all of the sections of the qualitative assessment and the interpretive rationale that forms the basis for the conclusion. Assumptions, uncertainties in the evidence, and other factors that may affect the relevance of the evidence to humans should be discussed. The conclusion should present both the weight-of-evidence ranking and a description that brings out the more subtle aspects of the evidence that may not be evident from the ranking alone.

III. Dose-Response Assessment, Exposure Assessment, and Risk Characterization

After data concerning the carcinogenic properties of a substance have been collected, evaluated, and categorized, it is frequently desirable to estimate the likely range of excess cancer risk associated with given levels and conditions of human exposure. The first step of the analysis needed to make such estimations is the development of the likely relationship between dose and response (cancer incidence) in the region of human exposure. This information on dose-response relationships is coupled with information on the nature and magnitude of human exposure to yield an estimate of human risk. The risk-characterization step also includes an interpretation of these estimates in light of the biological, statistical, and exposure assumptions and uncertainties that have arisen throughout the process of assessing risk.

The elements of dose-response assessment are described in section III.A. Guidance on human exposure assessment is provided in another EPA ***33997** document (U.S. EPA, 1986); however, section III.B. of these Guidelines includes a brief description of the specific type of exposure information that is useful for carcinogen risk assessment. Finally, in section III.C. on risk characterization, there is a description of the manner in which risk estimates should be presented so as to be most informative.

It should be emphasized that calculation of quantitative estimates of cancer risk does not require that an agent be carcinogenic in humans. The likelihood that an agent is a human carcinogen is a function of the weight of evidence, as this has been described in the hazard identification section of these Guidelines. It is nevertheless important to present quantitative estimates, appropriately qualified and interpreted, in those circumstances in which there is a reasonable possibility, based on human and animal data, that the agent is carcinogenic in humans.

It should be emphasized in every quantitative risk estimation that the results are uncertain. Uncertainties due to experimental and epidemiologic variability as well as uncertainty in the exposure assessment can be important. There are major uncertainties in extrapolating both from animals to humans and from high to low doses. There are important species differences in uptake, metabolism, and organ distribution of carcinogens, as well as species and strain differences in target-site susceptibility. Human populations are variable with respect to genetic constitution, diet, occupational and home environment, activity patterns, and other cultural factors. Risk estimates should be presented together with the associated hazard assessment (section III.C.3.) to ensure that there is an appre-

ciation of the weight of evidence for carcinogenicity that underlies the quantitative risk estimates.

A. Dose-Response Assessment

1. Selection of Data. As indicated in section II.D., guidance needs to be given by the individuals doing the qualitative assessment (toxicologists, pathologists, pharmacologists, etc.) to those doing the quantitative assessment as to the appropriate data to be used in the dose-response assessment. This is determined by the quality of the data, its relevance to human modes of exposure, and other technical details.

If available, estimates based on adequate human epidemiologic data are preferred over estimates based on animal data. If adequate exposure data exist in a well-designed and well-conducted negative epidemiologic study, it may be possible to obtain an upper-bound estimate of risk from that study. Animal-based estimates, if available, also should be presented.

In the absence of appropriate human studies, data from a species that responds most like humans should be used, if information to this effect exists. Where, for a given agent, several studies are available, which may involve different animal species, strains, and sexes at several doses and by different routes of exposure, the following approach to selecting the data sets is used: (1) The tumor incidence data are separated according to organ site and tumor type. (2) All biologically and statistically acceptable data sets are presented. (3) The range of the risk estimates is presented with due regard to biological relevance (particularly in the case of animal studies) and appropriateness of route of exposure. (4) Because it is possible that human sensitivity is as high as the most sensitive responding animal species, in the absence of evidence to the contrary, the biologically acceptable data set from long-term animal studies showing the greatest sensitivity should generally be given the greatest emphasis, again with due regard to biological and statistical considerations.

When the exposure route in the species from which the dose-response information is obtained differs from the route occurring in environmental exposures, the considerations used in making the route-to-route extrapolation must be carefully described. All assumptions should be presented along with a discussion of the uncertainties in the extrapolation. Whatever procedure is adopted in a given case, it must be consistent with the existing metabolic and pharmacokinetic information on the chemical (e.g., absorption efficiency via the gut and lung, target organ doses, and changes in placental transport throughout gestation for transplacental carcinogens).

Where two or more significantly elevated tumor sites or types are observed in the same study, extrapolations may be conducted on selected sites or types. These selections will be made on biological grounds. To obtain a total estimate of carcinogenic risk, animals with one or more tumor sites or types showing significantly elevated tumor incidence should be pooled and used for extrapolation. The